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| 論文題目 | PD-1/PD-L1 expression in a series of intracranial germinoma and its association with Foxp3+ and CD8+ infiltrating lymphocytes<br>（頭蓋内胚細胞腫において PD-1/PD-L1 の発現が Foxp3 陽性と CD8 陽性のリンパ球浸潤に関与する） | | |

（論文内容の要旨）

Central nervous system (CNS) germ cell tumors are common in Asia, where they account for 8-15% of all CNS tumors of childhood, compared to 3-4% in the United States. In about 10-20% of patients, the tumor recurs 10 years after first-line treatment. Thus, alternative therapeutic strategies for treating refractory tumors have become the main goals of current pediatric oncological efforts. Programmed cell death 1 (PD-1) is a receptor in the CD28 family, and plays an important role in immune tolerance and immune escape for a variety of tumor cells. However, the expression of PD-1 and its ligand PD ligand 1 (PD-L1) in intracranial germinoma remain unknown. Furthermore, large tumor cells of intracranial germinoma are frequently accompanied by an abundance of tumor-infiltrating lymphocytes (TILs), which suggests that immune escape mechanisms are involved in tumor development. The current work aims to investigate the expression of PD-1/PD-L1 axis and subtypes of TILs in intracranial germinoma.

Expressions of PD-1 and PD-L1 were detected immunohistochemically in 25 formalin-fixed, paraffin-embedded tumor specimens from 24 patients with intracranial germinoma, consisting of 22 primary and 3 recurrent tumors. In 25 tumor tissues, including all recurrent samples, expression of PD-1 in TILs was identified in 96% and PD-L1 in tumor cells was identified in 92%. High expression of PD-1 in TILs and PD-L1 in tumor cells were detected in 76% and 88%, respectively. In addition, PD-1 expression was not related to PD-L1 expression in the current cohort.

To evaluate subtypes of TILs, quantification of lymphocytes with CD3, CD8, CD4, and Foxp3 expression was performed. Widespread TILs of variable density with perivascular and dispersed foci were identified in intracranial germinomas. Among TIL subtypes, Foxp3+ TIL density was associated with CD3+, CD4+, and CD8+ TIL density, respectively. CD4+ TIL density correlated with CD8+ TIL density.

Associations between expression of PD-1 or PD-L1 and TIL subtype densities were evaluated. In 22 initial germinoma cases, CD3+ TIL density was significantly higher among patients with high expression of PD-1 than in those with low expression of PD-1. Higher Foxp3+ density and higher CD8+ TIL density in patients with high expression of PD-1 than in those with low expression of PD-1. However, no significant difference in CD4+ TIL density was evident between patients with high and low expressions of PD-1. Furthermore, Foxp3+/CD4+ ratio was higher in patients with high expression of PD-1 than in those with low expression of PD-1.

Univariate analysis with expressions of PD-1 and PD-L1 and clinicopathological parameters was performed in the 22 primary cases. Correlations between high expression of PD-1 in TILs and high serum β-hCG levels were identified. PD-L1 expression was stronger in patients < 18 years old. No other associations were found between other clinicopathological parameters and expressions of PD-1 or PD-L1.

This study revealed that PD-1 and PD-L1 expression were quite frequent in intracranial germinoma and were associated with Foxp3+ and CD8+ infiltrating lymphocytes. These findings suggest the breakdown of the tumor immune system that might be induced by PD-1/PD-L1 axis in intracranial germinoma.

（論文審査の結果の要旨）

アジア人に多く、小児期に好発する悪性脳腫瘍である頭蓋内胚細胞腫における PD-1/PD-L1 発現と腫瘍浸潤リンパ球を免疫組織化学的に解析した。頭蓋内胚細胞腫 25 例において、腫瘍浸潤リンパ球の PD-1 発現と腫瘍の PD-L1 発現は、それぞれ 96% と 92%で認めた。腫瘍浸潤リンパ球においては、Foxp3 陽性リンパ球数が CD3 陽性、CD4 陽性、CD8 陽性リンパ球数にそれぞれ関連していた。PD-1 高発現群では、Foxp3 陽性と CD8 陽性リンパ球数が高値であり、さらに Foxp3 陽性/CD4 陽性の比率も高値であった。単変量解析では、初発 22 例で PD-1 発現と血清中 β-hCG 高値、PD-L1 高発現と 18 歳以下の年齢に有意な相関を認めた。

本研究結果は、頭蓋内胚細胞腫において PD-1/PD-L1 発現が Foxp3 陽性と CD8 陽性の腫瘍浸潤リンパ球に関与することを示し、抗腫瘍免疫環境の変化が腫瘍発生・進行に関わる可能性を示唆した。

以上の研究は頭蓋内胚細胞腫の病態の解明に貢献し、PD-1/PD-L1 の発現が亢進した頭蓋内胚細胞腫に対する新たな治療法の開発に寄与するところが多い。

したがって、本論文は博士（　医学　）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、平成 30 年 7 月 9 日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公表可能日：　年　　月　　日　以降